cGAS-STING signaling in cancer immunity and immunotherapy

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ABSTRACT

Recent studies have shown that the innate immune cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway may play an important role in antitumor immunity. Additionally, the cGAS-STING pathway promotes the senescence of cancer cells, induces apoptosis of cancer cells, and increases the protective effect of cytotoxic T cells and natural killer cell-mediated cytotoxicity. We believe that the combination of the cGAS-STING signaling pathway with other therapeutic methods provides a new perspective from which to overcome obstacles in the application of this review. Further, we highlight the antitumor mechanism of the cGAS-STING signaling pathway and the latest advances in monotherapy and combination therapy with related agonists.

1. Introduction

Innate immunity is the host's first and fastest line of defense against invading pathogens. Host cells activate innate immune responses using different pattern-recognition receptors (PRRs) when they recognize conserved pathogen motifs known as pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). PRRs comprise a variety of system coding receptors that exist on the cell surface or in specific cellular compartments of the cytoplasm and significantly contribute to in the first step of recognizing invasive pathogens and mediating host defense. PRRs include Toll-like receptors (TLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs), nucleotide- binding oligomerization domain-like receptors (NLRs), retinoic acid-like receptors (RLRs), and cytosolic DNA receptors [1].

In eukaryotic cells, DNA is normally found in the nucleus and mitochondria. The presence of DNA in the cytoplasm is usually because of microbial infection or DNA damage. Thus, cytoplasmic DNA is a red flag that triggers a strong innate immune response. Recognizing cytoplasmic DNA is an important host defense mechanism. Cyclic GMP-AMP synthase (cGAS) is considered a key sensor in mediating cytoplasmic DNA recognition [2]. A key functional element of cGAS is its C-terminal nucleotide transferase (NTase) domain, which forms a bilobate structure consisting of a central catalytic domain and two independent positively charged surfaces [3]. Double-stranded DNA (dsDNA) can specifically activate cGAS to mediate the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signal transduction cascade. Two cGAS molecules combine with two dsDNA molecules to form a 2:2 cGAS - dsDNA complex [4]. Conformational changes in cGAS convert ATP and GTP to the second messenger cyclic GMP-AMP (cGAMP), which binds and activates the stimulator of interferon genes (STING) dimer located in the endoplasmic reticulum (ER), inducing the conformational change from the V-type to a more closed conformation. Thereafter, STING translocatesfrom the ER to the ER-Golgi intermediate compartment (ERGIC) and Golgi [5–7]. Two cysteine residues of STING (Cys88 and Cys91) are palmitated in the Golgi, promoting the recruitment of TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) [8]. TBK1 alone is not sufficient to activate IRF3; however, through mediation with a conservative consensus motif in STING, it can interact with IRF3 and phosphorylate STING and IRF3 [9]. STING also activates nuclear factor-kappaB (NF-κB) via inhibitor of NF-kappaB kinase (IKK). Subsequently, IRF3 and NF-κB are transported to the nucleus and drive the expression of type I interferon (IFN) and cytokines (Fig. 1).

Interestingly, STING binds directly to DNA, suggesting that it can also act as a direct cytoplasmic DNA sensor [10]. The physiological conditions, under which STING recognizes DNA and how it coordinates with other DNA sensors, remain to be further clarified.

A clinical study reported that STING expression is reduced and associated with reduced survival time in patients with gastric cancer [11]. In addition, bioinformatics analyses showed that low expression of cGAS is closely related to reduced survival time in patients with lung adenocarcinoma [12]. These findings have accelerated the interest

Abbreviations: CDN, Cyclic dinucleotides; CRMPC, Castration-resistant metastatic prostate cancer; DDR, DNA damage response; DMBA, 7, 12-dimethylbenzo(a) anthracene; DMXAA, 5, 6-dimethylxanthenone-4-acetic acid; ER, Endoplasmic reticulum; ERGIC, ER to the ER-Golgi intermediate compartment; HGSC, High-grade serous carcinoma; HNSCC, Head and neck squamous cell carcinoma; ICB, Immune checkpoint blocker; IDO, indoleamine 2, 3-dioxygenase; IFN, Interferon; IFNAR, IFN-α receptor; MTD, Maximum tolerated dose; NK, Natural killer; NSCLC, Non-small cell lung cancer; OS, Overall survival; PD, Pharmacodynamics; PFS, Progression-free survival; PK, Pharmacokinetics; RT, Radiotherapy; SASP, Senescence-associated secretory phenotype; SAVI, STING-associated vasculopathy with onset in infancy; SCLC, Small cell lung cancer; STING, Stimulator of interferon genes; TCGA, The Cancer Genome Atlas; TIS, Treatment-induced senescence.

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in exploring the relationship between STING agonists and cancer. STING agonists can also act in concert with a variety of traditional anticancer therapies, leading to tumor regression. In this review, we discuss the antitumor mechanism of cGAS-STING pathway, elaborated the preclinical and clinical application of STING agonists, and the profound significance of this pathway for new anticancer therapies.

2. Antitumor mechanisms of the cGAS-STING pathway

2.1. How does cytoplasmic DNA accumulate?

cGAS can detect intracellular cytoplasmic DNA and activate downstream IFN responses. The mechanisms of cytoplasmic DNA accumulation in antigen-presenting cells and tumor cells are not fully understood and may include micronucleus and mitochondrial DNA leakage caused by chromosome instability, DNA damage, and oncosuppressor gene mutation or deletion in cancer cells.

Methyl methanesulphonate and ultraviolet-sensitive 81 (MUS81) endonuclease can lead to chromosome instability through replication fork recognition and division stagnation, and are involved in the accumulation of cytoplasmic DNA in prostate cancer cells, inducing STING- dependent IFN and tumor rejection [13]. Besides activating the typical STING-dependent innate immune function in the cytoplasm, cGAS also exists in the nucleus in the form of chromatin binding proteins and inhibits DNA repair through homologous recombination; thus, promoting genomic instability and micronucleus production [14]. DNA damage may include endogenous DNA damage during mitosis or exogenous DNA damage caused by radiotherapy or chemotherapy drugs [15]. Sterile alpha motif and histidine-aspartate domain-containing protein 1 (SAMHD1) promotes the degradation of new DNA at replication forks of human cell lines by stimulating the exonuclear activity of MRE11 [16]. In SAMHD1-deficient cells, single-stranded DNA fragments are released from stagnant bifurcation and aggregated in the cytoplasm, activating the cGAS-STING pathway and inducing pro-inflammatory IFN expression [16].

DNA fragments from cancer cells exist in the tumor microenvironment and are absorbed by dendritic cells (DCs). Tumor DNA may also evade phagocytes through unknown mechanisms, enter the cytoplasm, and activate cGAS and STING [17].

2.2. Elimination of cancer cells via the cGAS-STING pathway

The immune system plays a key role in suppressing cancer. However, it is not clear how the immune system seeks cancer cells in the body. Recent studies have shown that the cGAS-STING pathway is crucial for immune monitoring of tumors. Cancer cells with chromosomal abnormalities or genomic DNA damage often form micronucleus or cytoplasmic chromatin fragments that activate cGAS in a cellular autonomic manner to initiate a cascade. This, in turn, promotes cellular senescence, induces apoptosis, enhances adaptive anticancer immunity, and inhibits or eliminates cancer cells.

2.2.1. Induction of senescence in cancer cells

The amount of stress that cancer cells are exposed to determines whether they advance toward apoptosis or senescence. When the level of cell damage is low, anti-proliferation responses associated with senescence, rather than cascade reactions, are triggered leading to apoptosis [18]. Senescent cells show characteristics of flattening, enlargement, nucleus protrusion, cytoplasmic particle size enlargement, and cell stagnation [18]. Cell senescence is considered as a mechanism of tumor inhibition to prevent abnormal proliferation of damaged cells.

The process of cell senescence passes through the early DNA damage response (DDR) stage and the senescence-associated secretory phenotype (SASP) response stage [19].Induction of cell senescence by oncogene activation are carried out in a cGAS-dependent manner. In many cell types, activation of oncogenes such as *RasV12* or *BRAFE600* leads to excessive DNA replication, increased replication errors, and initiation of DNA damage responses [20].This persistent DDR is considered to be one of the key mechanisms for the establishment and maintenance of aging phenotypes. Therefore, cGAS is recruited into the micronucleus to promote aging. Compared with the embryonic fibroblasts of wild-type mice, the embryonic fibroblasts of cGAS-/- mice show less senescence and faster spontaneous mortality [12]. cGAS is essential for cellular senescence, as deletion of cGAS leads to decreased expression of senescence inflammatory genes under the action of DNA damage agents [12]. Dou

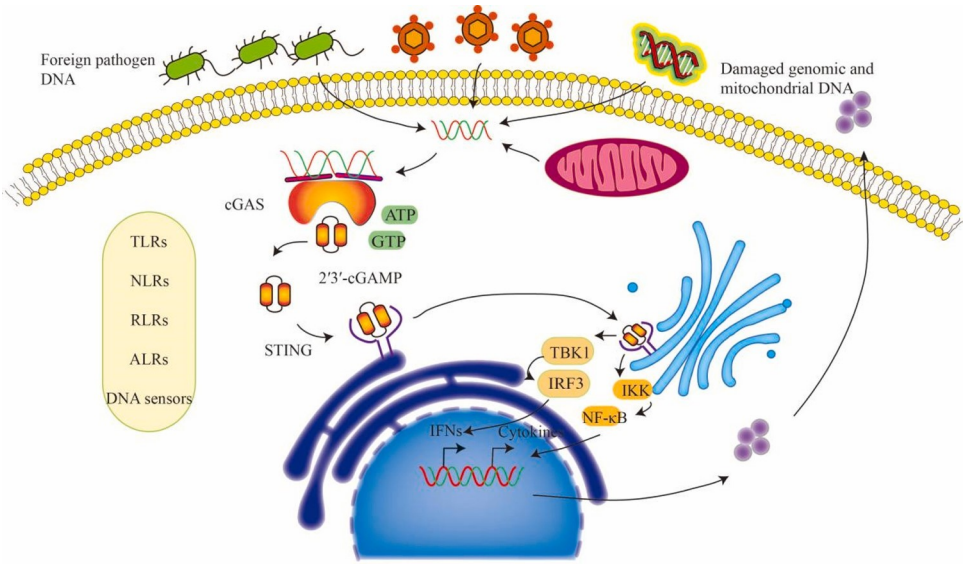

Fig. 1. The cGAS–STING signaling pathway. PAMPs from invading microbes activate PRRs, including TLRs, RLRs, NLRs, ALRs and DNA sensors. As a DNA sensor, cGAS can recognize cytoplasmic DNA from foreign microbes and damaged genomic and mitochondrial DNA. cGAS binds to dsDNA and converts ATP and GTP into the second messenger 2′3′-cGAMP, which binds and activates STING located in endoplasmic reticulum. STING translocates to Golgi, recruiting IRF3 and NF-κB via TBK1 and IKK,respectively.IRF3 and NF-κB translocate into the nucleus and drive the expression of IFN and cytokines. Abbreviation: PRRs, pattern- recognition receptors; RLRs, RIG-I-like receptors; NLRs, nucleotide-binding oligomerization domain-like receptors; ALRs, AIM2-like receptors; TLRs, Toll-like receptors; PAMPs, pathogen-associated molecular patterns; cGAS, cyclic GMP-AMP synthase; 2′3′-cGAMP, 2′3′- cyclic GMP–AMP.
STING, stimulator of interferon genes; IFN, interferon; NF-κB, nuclear factor-kappaB;IKK, inhibitor of NF-kappaB kinase.

et al. used the *RasV12* expression vector to induce liver tumors and found that the infiltration of early immune cells and removal rate of senescent cells in STING-deficient mice were reduced [21]. Type I IFN can amplify the DDR, activate the p55-P21 axis, increase p16INK4 levels, block the cell cycle, and promote senescence [22]. Therefore, the cGAS-STING pathway is one of the regulatory mechanisms that directly link the DDR to senescence.

The phenotypes of various proteins secreted by senescent cells (inflammatory cytokines, chemokines, and growth factors) are collectively referred to as SASP. cGAS is an important molecular link between DNA damage, SASP gene expression, and aging. cGAS, as an important indicator of the innate immune response, triggers SASP during the accumulation of cytoplasmic DNA (cytochromatin fragments, mtDNA, and cDNA) in senescent cells.In senescent cells, high transcriptional levels of long fragment-1 (LINE-1) reverse transcribe mRNA to cDNA in the cytoplasm, which promotes the accumulation of cDNA in the cytoplasm and triggers the cGAS-STING signaling pathway to produce SASP that induces reactive oxygen species and maintains cell senescence [19]. SASP factors are considered paracrine and autocrine enhancers that inhibit tumor growth during cell senescence to prevent the growth of damaged cells. Besides this function, SASP factors can recruit immune cells to eliminate senescent cells and stimulate the local immune response to eliminate oncogene-expressing cells [23]. They can also induce immune surveillance and act as tumor suppressors. However, SASP factors may cause tumorigenesis

because of exposure to chronic inflammation [20]. The positive and negative effects of SASP on cancer aging under different conditions need to be further clarified in future studies.

In addition to being a natural barrier to tumorigenesis, cGAS- mediated therapeutic senescence mechanisms contribute to the antitumor effects of a variety of therapeutic approaches, including radiotherapy and chemotherapy. DNA damage caused by radiotherapy and chemotherapy leads to the accumulation of cytoplasmic DNA and activation of the cGAS pathway, and the production of type I IFN leads to the amplification of DDRs that induce cellular senescence [22]. Compared with traditional cytotoxic treatment strategies, treatment-induced senescence (TIS) is a promising approach to induce tumor cell stagnation, permanently damaging the ability of cells to proliferate without causing cancer cell death [24]. This treatment has fewer side effects associated with cytotoxicity and is beneficial for the chronic treatment of some cancers. It is clinically significant that senescence-inducing drugs can act on inactivated tumor models via apoptotic signaling pathways, and that mice with drug-induced senescence tumors have better prognosis after chemotherapy than mice with senescence-defective tumors; this was confirmed in Eμ-myc lymphoma mouse model [25]. TIS have a surprising effect in solid cancers that are less prone to apoptosis or in which apoptotic pathways are blocked during tumor evolution [25].

Senescence is an endogenous barrier to malignant transformation, and tumor aging may imply a favorable outcome. In benign tumors such as nevi, lung adenomas, and other precancerous lesions such as prostate intraepithelial neoplasia, cells are often senescent; whereas, the senescence phenotype is absent in tumor cells [26–28]. The low expression of cGAS and STING in tumors may explain this. In benign tumors and precancerous lesions, relatively undifferentiated populations of cells can become senescent. If these cells represent cancer stem cells or important progenitor cell populations, cGAS-mediated senescence may hinder tumor progression by eliminating the proliferative capacity of these cell populations. Therefore, raising the question: Are precancerous lesions and early cancer cells more sensitive to anti-aging drugs than surrounding normal tissue? Moreover, the application of cGAS pathway-induced senescence in pre-cancer, early cancer, and late cancer is worthy of further study.

2.2.2. Promotion of cancer cell autophagy

Besides inducing IFN activity, STING can also induce autophagy activity to promote the clearance of cytoplasmic DNA, playing a crucial role in antiviral defenses. Autophagy is a process induced under various cellular stress conditions, such as hypoxia, nutritional deficiency, growth factor deficiency, and infection, to maintain the survival of cells or promote the apoptosis of senescent cells [29]. Autophagosomes form bi-membrane vesicles that isolate damaged organelles and protein aggregates, and invade intracellular pathogens for degradation in the cytoplasm [30]. When macrophages are infected with Mycobacterium tuberculosis, recognition of bacterial DNA through the STING pathway leads to ubiquitin-mediated autophagy, and the ubiquitin autophagy receptors P62, NDP52, and TBK1 transfer the bacteria to autophagosomes for degradation [31]. Beclin-1 autophagy protein, which interacts directly with cGAS, releases the negative autophagy regulator Rubicon, activates phosphatidylinositol 3-kinase III activity, and thus, induces autophagy to remove cytoplasmic pathogen DNA [32]. Chen et al. also found that cGAS-STING activates autophagy through WIPI2 and ATG5 [33]. Exogenous or endogenous damaged dsDNA stimulates cGAS to produce cGAMP, which combines with STING to recruit SEC24C for transfer from the ER to the ERGIC [33]. WIPI2-containing ERGICs are a membrane source of LC3 lipids and play a key role in autophagosome biogenesis [33]. LC3-positive membrane-coated dsDNA forms autophagosomes that are transferred to lysosomes and digested by various enzymes [33].

Autophagy induced by the cGAS pathway is crucial for the clearance of foreign viral DNA from the cytoplasm. Only a small number of cases of tumor-related DNA viruses in a large number of infected populations develop cancer, suggesting that the innate immune system, while not eradicating the virus, is effective in suppressing it in most cases. Owing to the continuous carcinogenic process of some viruses and bacteria that can lead to the development of cancer from initial infection to precancerous lesion and then to invasive tumor, it is important to study the expression profile of the STING pathway to distinguish productive infection from tumor-promoting infection in the process of chronic infection.

Moreover, STING-induced autophagy not only activates host defenses, but also regulates negative feedback regulatory mechanisms, preventing persistent innate immune activation and avoiding excessive production of inflammatory cytokines. There are at least three independent negative feedback regulatory mechanisms in the cGAS-STING pathway for avoiding cytokine storms, including Beclin-1 mediated inhibition of cGAS activity and cGAMP/P62-mediated inhibition of STING activity [31]. Beclin-1 autophagy protein interacting directly with cGAS inhibits cGAMP synthesis and prevents interferon production. Two autophagy mechanisms mediate STING degradation and impaired response [34]. One involves cGAMP, which induces activation of serine/threonine UNC-51-like kinase (ULK1) autophagy, phosphorylates STING, and promotes subsequent STING degradation [34]. The other is ubiquitination of STING autophagy mediated by phosphorylated P62/SQSTM1 [35]. STING mediates autophagy and autophagy degradation, thereby regulating the innate immune response.

2.2.3. Promotion of cancer cell apoptosis

The cGAS pathway can also promote apoptosis by transcriptional activation of apoptotic regulators and IRF3 [36]. In the STING pathway, the expression of proapoptotic protein BCL2-associated X (BAX) is upregulated, mediating mitochondrial

outer membrane permeability and caspase-3 activation driven by caspase-9, and promoting cell apoptosis [37]. The anti-apoptotic protein BCL2 is downregulated in the STING pathway [37]. The high expression of STING in T cells leads to the enhancement of the proapoptotic effect of two BH3 proteins, Noxa and Puma, controlled by IRF3 and p53 [36], respectively. It is worth noting that the proapoptotic response of STING also plays a role in malignant T cells [36]. TBK1 is the core regulator of the proapoptotic transcriptional program downstream of STING and also participates in the intrinsic apoptotic plan of T cells [36]. The application of STING's proapoptotic mechanism in treating T-cell-derived malignant tumors is a potential treatment method. Consistent with this view, T-cell apoptosis is increased in patients with STING-associated vasculopathy with onset in infancy (SAVI; carrying an overactive STING mutation) [38]. It could be interesting to explore if the STING-dependent apoptotic pathway can be exploited for other types of cancer cells.

During mitotic stagnation, slow accumulation of cGAS-dependent IRF3 phosphorylation does not induce inflammation but triggers transcription-independent apoptosis by reducing Bcl-xL's dependent inhibition of mitochondrial outer membrane permeability [39]. The cGAS pathway may provide potential benefits for some drug treatments that cause mitosis stagnation [39].

2.2.4. Enhancement of adaptive anticancer immunity

Cancer immune surveillance is thought to be mediated by immune cells such as natural killer (NK) cells and T cells. Fragments of DNA from cancer cells are present in the tumor microenvironment and are absorbed by DCs. These DNA fragments activate the STING pathway, induce the IFN response, and thus, activate DC maturation. Mature DCs, in turn, stimulate CD8 + T-cell activation. Increasing local DC maturation enhances tumor-specific T-cell responses. Defects in the IFN-α receptor (IFNAR) in DCs attenuate T-cell activation. It has been suggested that IFN plays a significant role in DC-activated antitumor immune responses [40] (Fig. 2).

The role of STING in cancer immune monitoring is not limited to DC activation. The expression of STING in tumor and host immune cells also inhibits the growth of melanoma by producing chemokines conducive to the infiltration of cytotoxic NK cells in the tumor microenvironment [41]. Extensive clinical evidence shows that NK cells have antitumor immunity in many cases because of the correlation between NK cells and other components of tumor infiltration [42]. NK cells can directly kill infected and transformed cells through the secretion of cytokines to form an adaptive immune response. IFN induces the expression of retinoic acid early transcript 1 (RAE1) ligands for NKG2D through DNA damage [43]. NKG2D ligands on tumor cells attract NKG2D + NK cells and activate CD8 + T lymphocytes, causing them to be destroyed and eliminated by the immune system [20]. cGAS in tumor cells is activated under steady-state conditions and can induce the spontaneous response of NK cells to tumor cells by activating the STING pathway [44]. The rejection of NK cells against tumor cells rather than abnormal cells in the body largely depends on the STING activation of non-tumor cells, and ultimately mobilizes a strong NK cell response to reject tumors [44].

3. Exploitation of the cGAS-STING pathway in immunotherapy

Just as pathogens have successfully evolved to co-exist with their hosts, cancer cells have evolved to evade their host's immune surveillance mechanisms. In theory, immunogenic tumors can be rejected by the immune system under optimal conditions of activating adaptive and non-adaptive antitumor immune responses [45]. In practice, however, most tumors evade recognition by the immune system and continue to grow in cancer patients. Successful immunotherapy requires overcoming the following tumor escape mechanisms: loss or downregulation of HLA I, mutation or loss of tumor antigens, changes in cell death receptor signaling, production of immunosuppressive cytokines, and inhibition of indoleamine 2, 3-dioxygenase (IDO) [45]. The loss of the cGAS-STING signal may also be a mechanism of tumor escape.

Cancer cells evolve to destroy the cGAS signal axis in order to avoid the recognition of cGAS innate immunity. In human colorectal carcinoma, ovarian cancer, and melanoma cell lines, the cGAS-STING pathway reduces related protein expression through various mechanisms, including not translocating STING to the Golgi, epigenetic silencing of cGAS-STING, and IFN locus mutation and loss, thus enabling the cancerous cells to bypass immune surveillance [46–49]. The cGAS-STING signaling pathway provides a new opportunity for overcoming the obstacles in the application of immunotherapy (Table 1).

3.1. Monotherapy

Besides the molecules directly bound to STING as agonists, soluble second messenger cGAMP and its derivatives are also used as important STING agonists. Demaria et al. demonstrated that intratumoral injection of cGAMP to activate STING in melanoma and colon cancer mouse models can enhance the antitumor CD8 + T response and delay the growth of tumors on the injection and contralateral side [51]. Tumor regression has been reported in many head and neck squamous cell carcinoma (HNSCC) models treated with STING agonists [54]. Importantly, using a STING agonist may help prevent the progression of precancerous lesions to HNSCC [68].

Exogenous cGAMP is an anionic water-soluble polymer. cGAMP is not confined to intracellular signals and can mediate a wider range of cell-immune cell transfers through gap junctions. Limitations on the use of cGAMP include drug delivery problems, poor cellular targeting, rapid clearance, low efficiency of cytoplasmic transport, and systemic

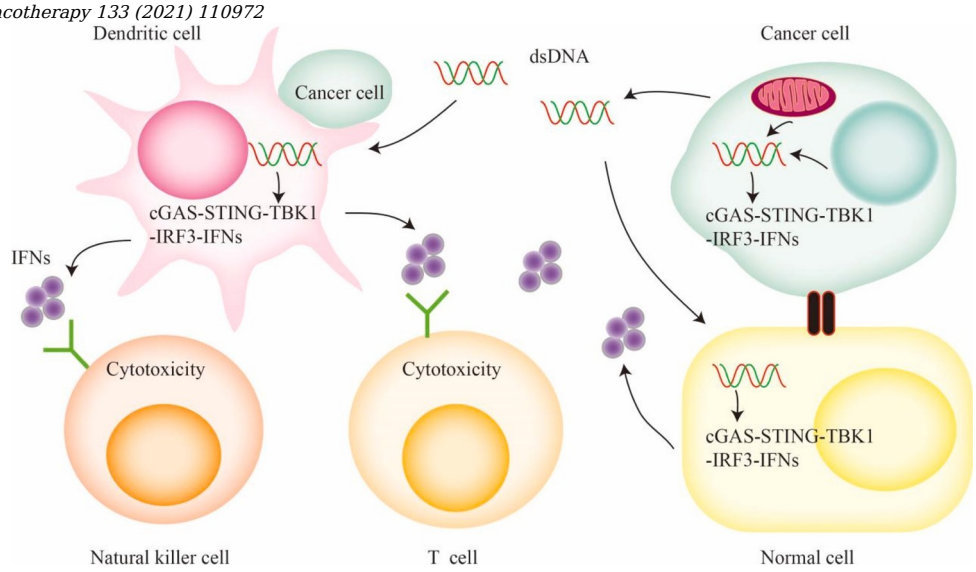

Fig. 2. Anti-tumor mechanism of cGAS-STING pathway.Fragments of DNA from cancer cells are present in the tumor microenvironment. These DNA fragments activate the STING pathway of DCs and normal host cells to induce IFN response, thereby activating the maturation of DCs. IFNs stimulate the activation of T cells and NK cells, and enhances the ability to kill tumor cells. Abbreviation:DCs:Dendritic cells; NK cells:Natural killer cells.

Table 1
The antitumor effect of cGAS-STING agonists.

Therapeutic Cancer type Agent delivery Antitumor effect Refs				
DMXAA	Mouse lung cancer, human lung cancer	Intravenous injection	Reduces tumor load	[50]
cGAMP	Mouse melanoma, colon cancer	Intratumoral injection	Delays tumor growth	[51]
STING-NPs	Murine melanoma, human metastatic melanoma tissue	Intratumoral injection, intravenous injection	Suppresses tumor growth	[52]
c-di-GMP/YSK 05-Liposomes	Mouse B16-F10 melanoma	Intravenous injection	Decreases metastasis	[53]
c-di-AMP combined with surgery	Murine HNSCC	Place dropwise into the surgical cavity	Controls residual lesions and distant metastasis	[54]
2′3′-c-di-AM (PS) 2 (Rp, Rp) combined with carboplatin	Murine ID8-Trp53− /− HGSC	Intraperitoneal injection	Prolongs the survival time of mice	[55]
IFN combined with cisplatin	Human breast adenocarcinoma MDA MB231 cell, mesothelioma cell, cervical cancer cells	Add drugs to cell culture medium	Inhibits tumor growth	[56,57, 58]
cGAMP combined with 5-FU	Murine colon adenocarcinoma	Intravenous injection	Inhibits tumor growth	[59]
2′3′-cGAMP combined with radiotherapy	Mouse colon cancer	Intratumoral injection	Tumor regression	[60]
DDR inhibitors combined with PD-L1blockade	Mouse SCLC	Subcutaneous injection	Inhibits tumor growth	[61]
c-di-GMP combined with CAR-T cells	Mouse pancreatic cancer	Place biopolymer scaffolds directly on pancreatic tumors	Tumor regression	[62]
cGAS-STING pathway defects combined with oncolytic viruses	Mouse colon cancer, ovarian cancer, melanoma	Intratumoral injection	Tumor regression	[46,47, 48]
Chitosan combined with H1	No specific cancer type	Intraperitoneal injection	Inhibits tumor growth	[63]
c-di-GMP combined with LM-based vaccine	Mouse breast cancer lung metastasis	Intraperitoneal injection	Inhibits tumor growth	[64]
c-di-GMP combined with TriVax vaccine	Mouse B16 melanoma	Intravenous injection	Inhibits tumor growth	[65]
STINGVAX combined with PD-1blockade	Mouse colon cancer	Subcutaneous injection	Reduces tumor volume	[66]
c-diAM(PS)$_2$ combined with STAT3 inhibitors	Mouse breast cancer lung metastasis	Intraperitoneal injection	Inhibits tumor growth	[67]

Abbreviation: DMXAA, 5, 6-dimethylxanthenone-4-acetic acid; cGAMP, cyclic GMP-AMP; STING-NPs, STING-activating nanoparticles; HNSCC, head and neck squamous cell carcinoma; LM-based vaccine, Listeria monocytogenes-based vaccine; MDSCs, Myeloid-derived suppressor cells.

inflammatory toxicity [52]. For this unique compound, the use of appropriately designed biomaterial delivery systems such as nanoparticles, virus particles, or targeted drug delivery can optimize treatment strategies, provide accurate administration of STING agonists to the tumor, generate local and specific antitumor immune responses, and significantly widen the treatment window.

To optimize cGAMP cytoplasmic transfer, Shae et al. designed STING-activating nanoparticles (STING-NPs). Intratumoral or intravenous injection of these enhances cGAMP biological activity, strengthens the STING signal transduction in the tumor microenvironment, and enhances tumor immunogenicity and inhibition [52].

Malignant melanoma evades immune surveillance by the loss or downregulation of MHC-I expression [53]. NK cells are potentially essential effector cells for melanoma elimination [53]. Intravenous injection of c-di-GMP coated by YSK05-liposomes in mice effectively induces the activation of NK cells and production of IFN, thus, producing a significant antitumor effect in mouse b16-F10

(MHC-I negative malignant melanoma) lung metastasis models [53].

The chemical therapeutic agent 5, 6-dimethyl xanthen1-4-acetic acid (DMXAA), first synthesized as an anti-vascular agent in 2002, can significantly reduce the tumor load by destroying the tumor vascular system [50]. In 2012, further studies showed that DMXAA targets STING and activates type I INF induction dependent on STING [69]. In order to determine DMXAA (ASA 404) toxicity, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor efficacy, cancer research centers in the UK and Auckland, New Zealand, carried out two parallel studies (NCT00863733) using DMXAA once a week and once every three weeks [70,71]. The patients were histologically confirmed cancer patients who were not suitable for standard or conventional treatment and were difficult to cure. They found that DMXAA showed good safety and tolerability within a large dose range and antitumor activity at tolerable doses. There was also no drug-related bone marrow suppression observed at low doses. A patient with metastatic cervical cancer achieved unproven partial remission at 1100 mg m^{-2} and progressed after eight courses of treatment [70]. The same unproven partial response occurred in patients with locally recurrent melanoma who received 1300 mg m^{-2} DMXAA [72].

MIW815 (ADU-S100) is also being clinically developed as single drug STING agonist. At the 2018 Cancer Immunotherapy Society meeting, MIW815 was reported to have treated 41 patients with advanced solid tumors at an increasing (starting dose: 50 μg) weekly intratumoral injection dose (3 weeks/1 week off) over a 28-day period [73]. A partial response was observed in 4.9 % of patients (n = 2/41; parotid gland adenocarcinoma, PD1 antibody-refractory; Merkel cell carcinoma, PD1 antibody-naive) [73]. Disease stability was achieved in 26.8 % of patients (n = 11/41) including five patients who had previously been treated with checkpoint inhibitors [73]. Trials in combination with anti-PD1 or anti-CTLA4 antibody (Ipilimumab) (NCT02675439) are ongoing.

E7766 is representative of a new type of macrocyclic bridging-linked stimulant, which has been proven to provide generic STING activation (in humans and mice) and effective anticancer activity with excellent chemical and metabolic stability. In 12 kinds of subcutaneous tumor mouse models, a single intratumoral injection achieved complete tumor regression or significant tumor growth delay without serious side effects [74]. Two Phase I E7766 studies are being conducted in patients with advanced solid tumor or lymphoma (NCT04144140) and non-muscular invasive bladder cancer (NCT04109092). In the dose-escalation portion of the study, the safety/tolerability of E7766 was assessed by intratumoral administration and the MTD and/or recommended Phase 2 dose (RP2D) for E7766 was determined. In the dose extension portion, E7766 was administered to melanoma, HNSCC, breast cancer, colorectal cancer, lymphoma, and non-muscle-invasive bladder cancer to confirm its safety and evaluate its preliminary clinical activity as a single drug.

In addition to STING targets, other key signaling molecules in the STING pathway can be used as targets of agonists. In contrast to STING agonists, activation of upstream cGAS enzymes produces amplified signals associated with STING receptor-small molecule interactions. Furthermore, the similar structure of human and mouse cGAS is more conducive to extrapolating mouse model results to clinical trials [49].
Therefore, cGAS agonists may be a better substitute for STING agonists. Activation of the STING pathway may be affected by microRNAs. Mir-378b and miR-29a can target TBK1 and IRF7 to activate the cGAS-STING signaling pathway [75]. MicroRNAs might be extensively studied as agonists in this pathway in the future.

3.2. Combination therapy

Growing evidence suggests that the STING pathway, as a potential drug target, could fundamentally contribute to the enhancement of current cancer treatments (surgery, radiotherapy, chemotherapy, and immunotherapy). Through the combination of the cGAS-STING pathway and different treatments, the positive aspects of the STING approach in treatment are maximized, the negative impacts are minimized, and good clinical results are achieved.

3.2.1. The STING pathway combined with surgery

Surgery is the most common intervention to eliminate primary tumors. The combination of stimulation of innate immune pathways and surgery can reduce local recurrence and inhibit distant metastasis [76]. As shown in clinical and preclinical models, immune mechanisms control minimal residual disease after surgical resection [76]. Baird et al. applied STING ligands to the resection edge of HNSCC and prevented local recurrence of HNSCC while being locally effective [54]. Therefore, the ability to enhance the tumor-specific adaptive immune response in the initial process is valuable for controlling residual lesions and distant metastasis [54]. Because the surgeon is in a unique position of being in direct contact with the tumor during the resection process, this provides an advantage for applying immunotherapy directly at the resection edge to activate the local immune mechanisms to target residual cancer cells [54].

The preclinical model shows that placing hydrogel containing the STING agonist at the site of tumor resection and extending the release of perioperative immunotherapy can prevent local tumor recurrence and induce systemic antitumor immunity, thus, eradicating existing spontaneous metastasis [77]. This has important implications in treating distant metastasis of advanced breast cancer, especially in the lung [77]. Combined application of STING therapy in HNSCC surgery may help prevent the progression of precancerous lesions to invasive lesions [68]. Moreover, STING therapy is effective for both STING + and STING- cancer [78].

Surgical excision of the tumor can improve the efficacy of immunotherapy by removing the concentrated immunosuppressive

microenvironment. STING therapy increases the number of NK cells, DCs, and T cells at the site of the tumor, and induces the production of large amounts of type I IFN. Combined immunotherapy can overcome the immunosuppressive state generated by surgery and transform the postoperative immunosuppressive microenvironment into immune stimulation.

3.2.2. The STING pathway combined with chemotherapy

The drug paclitaxel can stabilize microtubules and interfere with mitosis and is often used in cancer chemotherapy.The Cancer Genome Atlas (TCGA) dataset of patients with non-small cell lung cancer suggests that cGAS expression in tumors contributes to the response of patients with lung cancer and ovarian cancer to taxane drug treatment [39]. The expression of cGAS and IRF3 in tumor cells causes mouse-transplanted tumors to respond to the antimitotic drug paclitaxel [39]. During normal mitosis, the cGAS pathway is not effectively activated. During mitotic arrest, the slow accumulation of phosphorylated IRF3 that is not enough to trigger inflammation stimulates apoptosis by reducing the dependent inhibition of Bcl-xL on the permeability of the outer mitochondrial membrane [39]. cGAS and IRF3 play important roles in paclitaxel's inhibition of tumor growth. Whether the mechanism is directly mediated by mitotic cell death is unclear. Further trials are needed to determine the potential benefit of using the cGAS pathway as a combination therapy target for taxane therapy.

The standard treatment for the most lethal gynecologic malignancy, high-grade serous carcinoma (HGSC) of the ovary is tumor reduction surgery combined with platinum/taxane chemotherapy. Most patients initially show sensitivity to platinum; however, recurrence occurs in more than 70 % of the cases [55]. The mouse model of HGSC shows that a STING agonist combined with carboplatin treatment can inhibit tumor growth, reduce ascites accumulation, and prolong the survival time of mice [55]. Grabosch et al. reported that cisplatin therapy activates the STING pathway and enhances tumor immunogenicity-mediated tumor elimination by increasing calreticulin, MHC class I, antigen presentation, and T-cell infiltration [79]. Moreover, multiple studies showed that cisplatin combined with IFN can inhibit tumor growth more effectively than cisplatin alone [56–58].

5-Fluorouracil (5-FU) is a clinical antitumor drug that interferes with DNA synthesis. When used alone or in combination with adjuvant treatment of high-risk stage II and III colon cancer patients there are obvious side effects [59]. When used in combination with cGAMP, cGAMP can enhance the innate immune response by inducing the production of cytokines and stimulating the activation of DCs, which improves the antitumor activity of 5-FU and significantly reduces the cytotoxicity induced by 5-FU [59]. cGAMP alone is more suitable for patients with early colon cancer or for prevention of tumor recurrence or metastasis after chemotherapy or surgery [59]. cGAMP combined with chemotherapy can be used for high-risk stage II or III colon cancer patients [59].

In a Phase I trial (NCT01285453), nine Japanese patients with advanced or recurrent solid tumors received ASA404 (1800 mg/m^2) plus two doses of docetaxel (60 or 75 mg/m^2), administered every 3 weeks [80].The severity of adverse events was primarily level 1 or 2 and was usually associated with docetaxel treatment. Partial responses were observed in one patient, and five patients exhibited stable disease [80].

A randomized Phase II study (NCT00111618) assessed the use of ASA404 combined with docetaxel in 74 cases of castration-resistant metastatic prostate cancer (CRMPC) [81]. Patients not receiving chemotherapy and with histopathologically confirmed CRMPC were randomly assigned to receive docetaxel (75 mg/m^2) or docetaxel + ASA404 (1200 mg/m^2) for no more than 10 cycles [81]. The prostate-specific antigen response rate was higher in the combination group (59.4 % vs. 36.8 %) [81]. The tumor response rate was 23.1 % vs. 9.1 %, tumor progression time was 8.7 months vs. 8.4 months, median survival time was 17.0 months vs. 17.2 months, and 2-year survival rate was 33.3 % vs. 22.8 % on comparing the combined group with the docetaxel single group [81]. The combination of ASA404 and docetaxel is generally active in CRMPC. A retrospective analysis of the safety and efficacy of ASA404 (DMXAA) in 108 patients with squamous and non-squamous non-small cell lung cancer (NSCLC) in a Phase II study (NCT00832494) found that the addition of ASA404 with standard chemotherapy did not appear to significantly increase toxicity, and there were no serious adverse events associated with hemorrhage, pulmonary hemorrhage, or hemoptysis. Paclitaxel carboplatin + ASA404 appeared to have better activity than paclitaxel carboplatin alone, with median survival of 10.2 vs. 5.5 months and 14.9 vs. 11.0 months for squamous and NSCLC, respectively. This finding supports the inclusion of both groups of patients in the ongoing ASA404 deterministic phase III trial.

Although DMXAA showed excellent clinical prospects in preclinical stages I and II [82], it was regrettable that it failed in stage III clinical trials of NSCLC. The addition of ASA404 to carboplatin and paclitaxel, although generally well tolerated, did not improve the first-line efficacy of advanced NSCLC. There was no significant improvement in overall survival (OS), overall response rate (ORR), and progression-free survival (PFS). The small sample size of the Phase II trial may explain the different results by generating false positive signals. Later, it was found that DMXAA could not interact with human STING, which limited its potential application in human cancer immunotherapy [50]. Further research is needed to redefine and develop analogs of DMXAA that can bind to a human STING signal.

3.2.3. The STING pathway combined with radiotherapy

Besides surgery and chemotherapy, radiotherapy (RT) has been used for decades to treat various types of cancer. Preclinical and clinical

data show that the immune response after RT plays an important role in tumor control. Exogenous DNA damage caused by RT produces cytoplasmic DNA, which can enter the cytoplasm of DCs in the tumor, activating the STING pathway, inducing the generation of type I IFN, promoting the maturation of DCs, and triggering the activation of CD8 + T cells to support tumor regression [15]. The STING pathway is a key mediator of the tumor immune response to RT. When the STING pathway is combined with RT, exogenous cGAMP enhances STING signal transduction and promotes the antitumor effect of RT.

A decision is made whether to combine a STING agonist with RT according to the grading and selection of the radiation dose of the patients. Oxidative DNA modified by reactive oxygen species (ROS) induced by radiation from tumor cells and phagocytes can resist degradation mediated by the extracellular enzyme Trex-1, thus, ensuring the stability of the transmission of tumor cell DNA to the cytoplasm of DCs [83]. The DNA exonuclease Trex-1 is induced by radiation doses above 12–18 Gy in different cancer cells and reduces its immunogenicity by degrading the DNA accumulated in the cytosol after RT [60]. Repeated dose irradiation below the induced dose threshold of Trex-1 can effectively stimulate the production of IFNβ by the STING pathway in cancer cells [60]. When the radiation dose cannot stimulate the cancer cells to produce their own IFNβ for treatment, it is necessary to insert the STING agonist inside the tumor to induce IFNβ and improve the tumor response [84]. These studies suggest ideas for a better understanding of the mechanism of radiation-mediated tumor regression and its integration with current immunotherapy methods, laying the foundation for new strategies for selecting the optimal timing, dosage, and tissue target for RT and STING therapy. It is imperative to optimize RT for activating innate signals and promoting antitumor immune responses.

3.2.4. The STING pathway combined with other immunotherapies

3.2.4.1. The STING pathway combined with immune checkpoint blocker therapy. Immune checkpoint blockers (ICBs) mainly target cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD-1), or its main ligand PD-L1 [85]. These immune checkpoint inhibitors have been approved for the routine clinical treatment of many cancers, although their response rates and efficacy remain low. ICB drugs show different activities in different cancer types with primary and adaptive drug resistance [86]. A large amount of evidence shows that the efficacy of immunotherapy is highly dependent on tumor immunogenicity, the abundance of intratumoral antigen expression, and tumor immunoinfiltration [87]. Most patients do not respond to ICBs because their tumors are less immunogenic and do not elicit an adequate immune response.

To enhance tumor response to ICB treatment, it is necessary to find a combination of drugs that can increase tumor immunogenicity and promote the killing of cancer cells and immune infiltration in the body. Injecting STING agonist directly into the tumor can improve the immunogenicity of the tumor by promoting antigen presentation and activate DCs and antitumor T cells to regulate the tumor microenvironment and transform the immune "cold" tumor into "hot" tumor [88]. A preclinical model showed that teniposide, a DNA topoisomerase II inhibitor, enhanced the antitumor effect of anti-PD1 through the STING pathway [40]. Patients with small cell lung cancer (SCLC) are usually associated with relatively high immunosuppression and low T-cell infiltration, and clinical trials of blocking PD-1 or PD-L1 show a low ORR [87]. DDR inhibitors activate the function of cytotoxic T lymphocytes by activating the STING pathway and increasing the expression of IFN and chemokines CXCL10 and CCL5, and ultimately enhance the antitumor effect of PD-L1 blockade. Combining DDR inhibitors and ICBs for treating SCLC has shown therapeutic potential [61].

PARP inhibitors (PARPis) have been approved for treating ovarian and breast cancer patients with BRCA1/2 mutations. Compared with standard chemotherapy, PARPis increase the response rate and PFS [89]. DNA damage mediated by PARPis leads to the accumulation of dsDNA in cells, amplifying the STING signal to increase immunogenicity and sensitivity to ICBs [90]. However, the PARPis-dependent STING pathway response is limited, and STING agonists are the preferred combination partners for ICBs.

In 2018, the European Society of Medical Oncology meeting reported 26 cases of single treatment using a STING agonist (MK-1454; intrathecal injection for nine weeks, once a week, and then once every three weeks) and 25 cases of combined treatment with pembrolizumab (200 mg intravenous injection every three weeks) with advanced-grade solid tumors or lymphomas stage I (NCT03010176). Preliminary assessment of disease control rates revealed 48 % for combination therapy and 20 % for monotherapy. It is encouraging that MK-1454 is efficient in combination with pembrolizumab and has acceptable levels of safety [91].

Spartalizumab (PDR001) is a humanized IgG4 monoclonal antibody that blocks the binding of PD-1 to PD-L1/2. Partial responses were observed in patients with pD-1-naive triple negative breast cancer and PD-1 recurrent/refractory melanoma in a Phase Ib study (NCT03172936) of patients with advanced/metastatic solid tumor or lymphoma who received MIW815 (ADU-S100; intratumoral injection 50–800 μg, three weeks on/one week off) and Spartalizumab (intravenous injection 400 mg, once every four weeks). A Phase II trial is currently under way (NCT03937141).

3.2.4.2. The STING pathway combined with CAR-T therapy. In the field of immune cell therapy, chimeric antigen receptor T (CAR-T) cell therapy has been gradually attracting attention. The basic principle involves the specific recognition of the target antigen on the surface of tumor cells to specifically kill tumor cells through the activation of intracellular signals [92]. To date, CAR-T cells have been very effective in treating hematological tumors [92]. However, CAR-T cells show poor

results in the treatment of solid tumors [92]. The complex immunosuppressive microenvironment of solid tumors, highly heterogeneous tumor parenchyma, and limitations of immune target selection are the causes of these results [93]. Recent studies have shown that the combination of STING agonists and NKG2D CAR-engineered T cells containing anti-CD3, anti-CD28, and anti-CD137 has significant effects in controlling pancreatic tumors, and the tumor microenvironment changes from one of inhibition to one of tolerance [62]. This discovery has helped shrink inoperable tumors and enable patients to become eligible for further intervention measures.

3.2.4.3. The STING pathway combined with oncolytic virus therapy. Oncolytic virus therapy is a new type of antitumor therapy. It usually uses genetically engineered viruses that selectively replicate and dissolve cancer cells without affecting normal cells. This induces systemic antitumor immunity, which can be used to treat advanced malignant tumors [94]. In view of the important role of cGAS-STING in the host's defense against viral infections, it is worth exploring the application of oncolytic viruses. Supporting this view is that dsDNA viruses, such as vaccinia virus, adenovirus, and herpes simplex virus type 1, can activate the cGAS-STING pathway [49].

In normal cells, the STING pathway can detect and eliminate pathogenic virus particles, hindering the effectiveness of virus replication and oncolytic activity. However, virus clearance is obstructed in colon cancer, ovarian cancer, and melanoma cancer cell lines harboring cGAS- STING pathway defects. Oncolytic viruses are more likely to infect these cell lines and exhibit stronger oncolytic activity in these cell lines [46, 47,95]. Most oncolytic viruses manipulate different abnormal signal transduction factors in tumor cells to prevent cell apoptosis [94], and the virus induces cell death only after replication. In addition to directly eliminating tumor cells, tumor-associated antigens released after the death of oncolytic cells can promote adaptive immune responses and mediate the regression of distant tumors that have not been exposed to the virus [94]. Therefore, for cancers with defective cGAS or STING function, the use of oncolytic viruses is a potential strategy against this immune evasion mechanism. By evaluating the expression level of cGAS or STING in biopsy specimens, we can better predict the therapeutic effect of oncolytic virus.

3.2.4.4. The STING pathway combined with cancer vaccines. Cancer vaccines can be used to train the immune system to selectively destroy cancer cells, providing better options for preventing or treating metastatic cancer [96]. However, cancer vaccines have limitations. First, vaccine-induced responses may take a long time to mature, making it difficult to control advanced disease [96]. Second, they are hindered by tumor microenvironmental immunosuppression [96].

To increase the effectiveness of vaccines, various vaccine adjuvants that stimulate innate immunity and reduce immunosuppression have been developed. Adjuvants that rely on the STING pathway have shown potential in vaccinology. Some existing vaccine adjuvants, such as chitosan, rely on the STING pathway to enhance antigen-specific T helper 1 (Th1) responses [63]. Moreover, cyclic dinucleotides (CDNs; c-di-AMP and c-di-GMP), the second messenger molecules of bacteria, are potent anticancer vaccine adjuvants [97]. In vitro studies have shown that c-di-AMP stimulates pre-activated mouse macrophages and promotes the activation and maturation of mouse and human DCs [98].

Myeloid-derived suppressor cells (MDSCs) are one of the most important cells mediating tumor microenvironment-related immunosuppression, which can strongly inhibit T cells and NK cells [99]. A breast cancer metastasis model (4T1 model) shows that using the STING ligand c-di-GMP as an adjuvant for Listeria monocytogenes (LM)-based vaccines can overcome immunosuppression and target MDSCs and tumor cells to improve the vaccination effect [64].

Clinical trials of patients with advanced melanoma showed that the clinical response rate and OS time after cancer vaccination did not improve significantly [65]. The reason may be the poor immunogenicity of the vaccine and insufficient number of antigen-specific CD8 + T cells produced. Wang et al. found that c-di-GMP enhanced the immunogenicity and antitumor effect of a peptide vaccine (TriVax vaccine) in mouse B16 melanoma [65]. CDNs can increase IFN-I secretion and activate the NF-κB signaling pathway to enhance vaccine-induced T-cell activation [65]. The cancer vaccine STINGVAX (ML-RR-S2-CDA) uses CDNs as adjuvants for cells secreting granulocyte-macrophage colony-stimulating factor and has the ability to inhibit tumor growth in a variety of cancer treatment models [66]. Furthermore, STINGVAX directly causes lymphocyte tumor infiltration and high expression of PD-L1 in the tumor microenvironment [66]. As an effective inducer of PD-L1 secretion in the tumor microenvironment, STINGVAX is highly suitable for clinical application in combination with ICBs, especially anti-PD-1.

In addition to CDNs, TBK1, an adjuvant of DNA vaccines, is a key signal molecule for inducing immunogenicity [100]. Data have shown that TBK1 plays a crucial role in the induction of antigen-specific B, CD41 T, and CD81 T cells in hematopoietic and non-hematopoietic cells, respectively [100].

3.2.5. The STING pathway combined with other new strategies

Pei et al. found that inhibition of the STAT3 pathway significantly enhances the intensity and duration of the STING signal induced by STING agonists [67]. This sensitization effect mainly depends on STAT3, which inhibits various regulatory factors that regulate STING protein rather than STAT3 itself, inhibiting STING signal transduction [67]. Moreover, compared with single therapy, the combined application of STAT3 inhibitors and STING agonists c-diAM$(PS)_2$ increases CD8 + T cells and reduces regulatory T cells (Tregs) and MDSCs in the tumor microenvironment, and significantly inhibits tumor growth in mice [67]. This provides a theoretical basis and potential new

strategies for the combined application of STAT3 inhibitors and STING agonists in cancer immunotherapy.

In human papillomavirus (HPV) 18+ cervical squamous cell carcinoma cells and HPV 16 + HNSCC cell lines, it was found that the viral oncogene E7 of a DNA tumor virus combined with STING inhibited its pathway activation [68,99]. In vivo models show that STING agonists influence HNSCC tumor regression [68]. In the future, the combined application of drugs targeting the HPV E7 oncogene and STING agonists for HPV + cancers (cervical cancer and HNSCC) is a direction worth investigating.

4. STING immunotherapy: a double-edged sword

The STING pathway has become a promising drug target for cancer treatment. However, owing to its dual role in tumorigenesis and immunity, its application in treatment is overly complicated. Severe side effects, including autoimmune and inflammatory reactions, and direct tissue toxicity, limit the antitumor potential of exploiting the STING signaling pathway [101].

Chronic stimulation of the STING pathway may promote inflammation-driven tumorigenesis. Studies show that STING can increase the levels of inflammatory cytokines in infiltrating phagocytes and promote inflammation [101]. Activation of the STING pathway was found in 7, 12-dimethylbenzo(a)anthracene (DMBA) chemicallyinduced skin cancer [102]. The levels of inflammatory cytokines are subsequently increased by infiltrating phagocytes to clear dead cells in a STING-dependent manner and promote skin tumors [102].Compared with wild-type mice, STING-/- mice or wild-type mice transplanted with STING-/- bone marrow almost completely resist skin carcinogenesis induced by DMBA [102]. It is, therefore, preferable to avoid the high levels or sustained action of STING agonists that cause uncontrolled activation of STING, leading to continuous inflammation and cancer. Determining the optimal STING agonist level to ensure that it contributes to the induction of a strong antitumor immune response and does not activate inflammation-induced carcinogenesis is extremely important in cancer treatment.

Factors such as tumor type, tumor microenvironment, tumor immunogenicity, and agonist properties may affect STING-mediated immunotherapy. When the tumor has low antigenicity, the activation of the STING pathway in the tumor microenvironment induces an increase in IDO activity, which promotes the growth and immune escape of Lewis lung cancer [103]. STING agonists are more suitable for tumors with higher antigenicity than weakly immunogenic tumors. Besides participating in the occurrence of inflammatory tumors and immune evasion, the cGAS-STING signal may be involved in tumor metastasis. cGAMP transferred by tumor cells through gap junctions activates STING in astrocytes and promotes the growth of metastatic brain cancer cells [104]. Brain metastatic cancer cells use gap junctions to transfer the second messenger cGAMP to astrocytes, activate the STING pathway, and produce inflammatory cytokines, such as IFN-α and tumor necrosis factor [104]. These paracrine signals activate the STAT1 and NF-κB pathways in brain metastatic cancer cells, thereby supporting tumor growth and drug resistance [104]. Therefore, further research is needed to determine the tissue specificity of STING-mediated immunotherapy.

5. Conclusions

Cancer immunotherapy eliminates tumor cells by enhancing multiple steps in the tumor immune cycle, including antigen presentation and T-cell activation, and activating immune killing activity. The innate immune cGAS-STING pathway promotes the maturation and migration of DCs, enhancing cytotoxic T lymphocytes or NK cells to mediate cytotoxic effects and protecting effector cells from apoptosis. Various agonists, including STING-binding molecules and CDN derivatives, have been explored with respect to antitumor immunity and for their therapeutic effects in the context of both monotherapy and combination therapy.

However, considering that the activation of the cGAS-STING pathway is also associated with tumor metastasis and autoimmune diseases, the timing and side effects of treatment must be considered before using the agonists in cancer therapy. Prior to the clinical application of anticancer immunotherapy based on the cGAS-STING pathway, it is necessary to conduct an in-depth and comprehensive evaluation of the role of this pathway in different types of tissues to achieve a good balance between obtaining an optimal antitumor effect and minimizing the pro-tumor inflammatory response. Long-term use of cGAS-STING pathway activators for treatment requires careful formulation of the dose and medication interval plan to avoid continuous activation of the pathway, which leads to inflammation and organ damage.

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Declaration of Competing Interest

The authors report no declarations of interest.

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